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## REVIEW ARTICLE OPEN



# In silico modelling of cancer nanomedicine, across scales and transport barriers

Namid R. Stillman<sup>1</sup>, Marina Kovacevic<sup>2</sup>, Igor Balaz<sup>3</sup> and Sabine Hauert<sup>1</sup>✉

Nanoparticles promise to improve the treatment of cancer through their increasingly sophisticated functionalisations and ability to accumulate in certain tumours. Yet recent work has shown that many nanomedicines fail during clinical trial. One issue is the lack of understanding of how nanoparticle designs impact their ability to overcome transport barriers in the body, including their circulation in the blood stream, extravasation into tumours, transport through tumour tissue, internalisation in the targeted cells, and release of their active cargo. Increased computational power, as well as improved multi-scale simulations of tumours, nanoparticles, and the biological transport barriers that affect them, now allow us to investigate the influence of a range of designs in biologically relevant scenarios. This presents a new opportunity for high-throughput, systematic, and integrated design pipelines powered by data and machine learning. With this paper, we review latest results in multi-scale simulations of nanoparticle transport barriers, as well as available software packages, with the aim of focussing the wider research community in building a common computational framework that can overcome some of the current obstacles facing efficient nanoparticle design.

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## INTRODUCTION

For over three decades, nanomedicine has held the potential to prevent, delay, control, or even cure cancer. Over two-thirds of nanomedical research has been focused on oncology<sup>1–3</sup>. Starting with Doxil in 1995, there are now around a dozen FDA-approved anti-cancer nanoparticles<sup>4</sup>. Nanoparticles, typically between 1 and 100 nm in size<sup>5</sup>, have been shown to be effective drug-vectors thanks to their ability to shield therapeutic cargos throughout transport, accumulate in certain tumour types<sup>6</sup>, activate through environmental (e.g. pH, enzymatic activity) or external stimuli (such as magnetic resonance, ultrasound, or infrared light<sup>7–9</sup>), or target specific cells<sup>10</sup>. Active targeting includes designs where the nanoparticle surface is functionalized to bind to target receptors or other proteins expressed on the membrane of the cancer cells, the extracellular matrix (ECM), or tumour vasculature. On the other hand, passive targeting is mediated by the size of nanoparticles, which is thought to favour their accumulation at certain tumour sites due to the EPR effect<sup>6</sup>. Increasingly sophisticated nanoparticle functionalisation, or combination strategies, are being explored as mechanisms to make treatments both smarter and more effective<sup>11</sup>.

The versatility of nanomedicine is a result of the vastness of the design space for nanoparticles. Changing the behaviour of nanoparticles can be achieved by altering the conventional 4S parameters, namely size, shape, surface functionalisation and stiffness<sup>12</sup>. The surface functionalisation in particular contributes to the charge of the particle, its stability in (and clearance from) the bloodstream, as well as active targeting. Further specifications include the material used (for example, energy receptive or reactive to the environment), and the loading of the drug (such as chemotherapy).

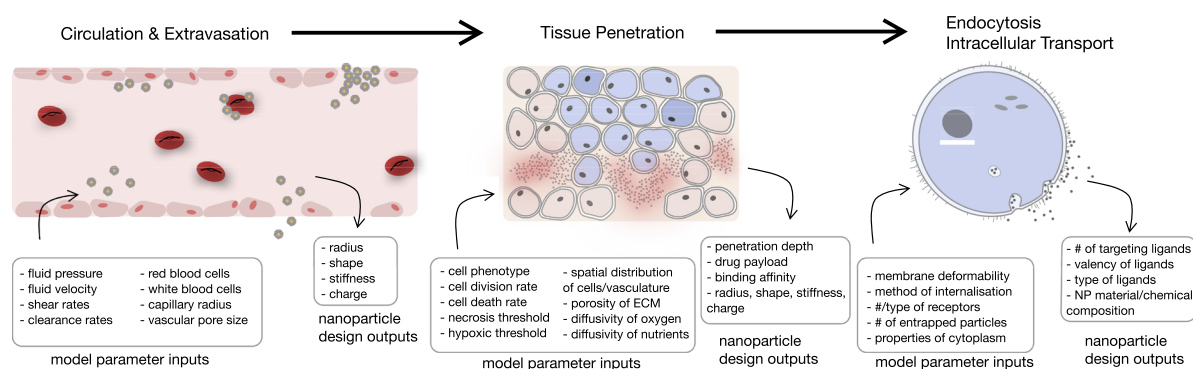
Key to predicting clinical impact, such as the correct distribution of nanoparticles over a tumour, relies on an accurate understanding of the interaction between individual nanoparticles and

their environment. These interactions can motivate coordinated strategies, where sub-populations of nanoparticles might alter their local environment (such as degrading the ECM<sup>13</sup>), amplify signals to other nanoparticles<sup>14</sup>, create anchored binding sites for other nanoparticles, or self-assemble/disassemble to improve transport<sup>15,16</sup>. Such coordinated strategies, sometimes inspired by swarm intelligence<sup>11</sup>, demonstrate the high degree of customisability inherent to nanoparticle design. While this customisability can lead to novel nanoparticle strategies, their discovery and validation can be a challenge.

Despite, or perhaps because of, the many design parameters that can alter the functioning of nanoparticles, many prototypes fail to realise success as an alternative (or supplement) to conventional treatment techniques. Though many pre-clinical trials demonstrate increased specificity, only 5% of the dose typically reaches the tumour site during clinical trials<sup>17</sup>. Transport barriers to the target site are expected to play a key role in this disappointing result, including travel through the circulatory system and avoiding clearance, extravasation to the tumour site, tissue penetration within the tumour, and delivery to the relevant part of the cell.

Recent advances in computational power, as well as improved simulations of nanoparticles, and the biological transport barriers that affect them, allow for multi-scale simulations that can investigate the influence of a range of parameters in biologically realistic scenarios. This presents a new opportunity for high-throughput, systematic, and integrated nanoparticle-design pipelines. Such future pipelines may enable general design principles which, when combined with patient-specific data, could provide personalised treatment and care. Furthermore, utilisation of in silico models can minimise the costs associated with more conventional trial and error approaches in the laboratory, especially when combined with recent machine learning techniques such as 'active learning'<sup>18</sup>.

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**Fig. 1 Multi-scale modelling of nanoparticles (NPs) to overcome transport barriers.** Models take barrier scenarios as input, and output suitable NPs designs. Several example inputs and outputs are provided for each barrier, though the list is not intended to be exhaustive.

There are now many computational models and results that have been reported on different stages of tumour initiation, growth, and the interaction of nanoparticles within the body and tumour. Below, we summarise some of the most recent and relevant *in silico* models for overcoming nanoparticle transport barriers. We focus predominantly on cancer nanomedicine, but note that many of the models we describe are relevant to other cancer therapies that may not use nanoparticles, such as immunotherapy or chemotherapy, as highlighted in several reviews<sup>19–21</sup>.

Many of the *in silico* models that we describe have been integrated with *in vitro* and *in vivo* experiments, as well as with machine learning techniques. We believe that a systematic and integrated framework for drug development, building on these examples, can minimise costly trial-and-error approaches and accelerate the development of effective nanoparticle cancer therapies. However, such a framework requires a shared modelling language and a multidisciplinary approach, with ongoing collaboration between mathematical and computational modellers, experimentalists, and clinicians. This paper is an attempt to provide a comprehensive review that sets the stage for such a pipeline, as we detail in our concluding remarks.

## IN SILICO MODELS OF TUMOURS

Central to *in silico* modelling of nanoparticle treatments is having realistic models of the tumours. Malignant tumours caused by the uncontrolled proliferation of faulty cells, can be separated into three groups; carcinomas, leukomas, and sarcomas. Of the three groups, carcinomas are the most common (accounting for 90% of reported cases<sup>22</sup>) and predominantly appear in certain cell types such as breast, lung, prostate, and colon/rectum. These cell types alone accounted for more than half of all cancers reported in the USA in 2018<sup>23</sup>. Carcinomas are typically large, greater than 1 cm<sup>3</sup> when detected, and fatal if left untreated<sup>22</sup>. They are the main topic of this paper.

Existing mathematical approaches<sup>24</sup> can be separated into three groups: continuum, discrete, and hybrid. The continuum models, which utilise ordinary and partial differential equations, are typically faster to compute and are better suited to capturing global changes to a tumour, such as availability of oxygen and nutrients (e.g. to predict the development of a hypoxic core in a solid tumour). However, they are limited in their ability to recreate heterogeneity, single-cell interactions and other features better suited to a discrete modelling approach such as agent-based (AB), cellular potts (CP), and cellular automata (CA). Discrete models focus on the individual units (such as the cell) that follow a simple set of rules guiding their growth, death, and interaction with the local environment and other agents. This could be used to model the realistic heterogeneous development of a tumour over time,

how cellular resistance emergence, or the growth of angiogenic vessels.

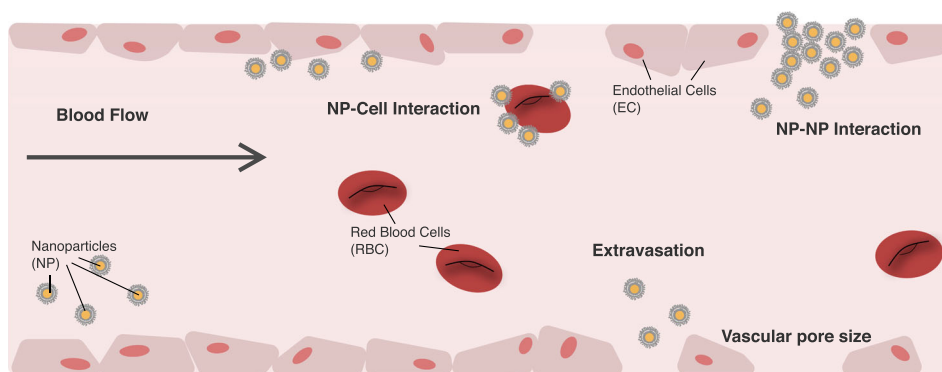
Both approaches have their strengths and weaknesses, and this has led some researchers to combine both continuum and discrete approaches to gain the benefits of both, so-called hybrid methods. Hybrid models build on discrete models but combine them with gradients of variables, modelled using continuum equations<sup>25</sup>. These models are also able to monitor individual cell behaviour such as mutation as well as the influence of local environmental variables. For a review of discrete and hybrid models and their application to cancer, see, for example work by Kim et al. and An et al.<sup>26,27</sup>, for multi-scale cancer modelling, see work by Deisboeck et al. and Norton et al.<sup>28,29</sup>, and for agent-based cancer models, see work by Metzcar et al.<sup>30</sup>.

## MODELLING TRANSPORT BARRIERS FOR NANOPARTICLE DELIVERY

The use of nanoparticles as drug-delivery vectors requires that the engineered particles navigate from point of entry into the body to their prescribed biological target. The nanomedicine is normally administered topically, orally, intravenously or through direct injection to the site (e.g. to overcome the blood-brain barrier). Transportation barriers will present themselves immediately. Effective use of NPs requires overcoming these transport barriers: travel through the vasculature<sup>31–33</sup>, extravasation<sup>34–36</sup>, avoiding uptake by the reticulo-endothelial system (RES)<sup>37–39</sup>, progression through the tumour tissue<sup>35,40–44</sup>, endocytosis<sup>45–50</sup>, and delivery to the relevant part of the cell<sup>51–53</sup>. While each of these barriers presents a considerable individual challenge, the optimum NP design must seek to overcome several (if not all) of them to reach maximum efficacy. However, the high number of parameters that can be altered when designing nanoparticles results in a rich design space which is difficult to optimise, as shown in Fig. 1.

## CIRCULATION, CLEARANCE (CC) AND EXTRAVASATION (EV)

For intravenously injected nanoparticles, remaining in the blood stream as long as possible (long half-life) will favour their accumulation in certain types of tumours that benefit from the leaky nature of angiogenic blood vessels. The longer the circulation time, the higher the probability of escaping into the tumour site through multiple arrival ports (as opposed to a single one with direct injection<sup>54</sup>). Several direct factors influence circulation time including nanoparticle size, shape, and charge. Nanoparticles that are smaller than 5 nm are quickly cleared by the kidneys<sup>55</sup>. Nanoparticles larger than 100 nm are more likely to be detected by macrophages and cleared<sup>56</sup>. Between 5 and 100 nm, the charge of nanoparticles and resulting protein corona, or opsonisation, will drive macrophage uptake<sup>57</sup>. *In silico* methods such as molecular dynamics simulations have been used to



**Fig. 2** Considerations when modelling nanoparticle (NP) transport through the vascular chamber, as well as extravasation of NPs through the endothelial wall. Here, NPs are shown travelling through the vascular chamber, where they interact with cells (such as red blood cells) as well as other NPs. Eventually, NPs leave the vessel through extravasation.

examine the influence of these factors (such as protein corona formation and pH-stability) on nanoparticle transport<sup>58–60</sup>. For a further review of factors that affect circulation time for nanoparticles, see, for example, work by Yoo et al.<sup>61</sup>.

There are other influencing factors that can affect nanoparticle transport through the vascular system, as shown in Fig. 2. For example, margination occurs when red blood cells segregate in the centre of the vessel, creating a ‘cell-free’ layer near to the vessel wall<sup>57</sup>. This allows for nanoparticles to more readily escape from the porous tumour vessel by avoiding interactions with the blood cells and was demonstrated *in silico*, using a combination of dissipative particle dynamics (DPD) (a coarse-graining approach) and computational fluid dynamics<sup>62</sup>. By modelling the interaction between nanoparticles, red blood cells and white blood cells in the vessel, it was shown that the larger nanoparticles (greater than 500 nm) are able to take advantage of this margination effect whereas smaller nanoparticles (less than 200 nm) are trapped with the red blood cells in the ‘core’ region<sup>12</sup>.

Alternatively, the clustering of red blood cells may prove an important factor in increasing the biodistribution of nanoparticles, as clustering behaviour has been observed to create small variations in the capillary radius that can lead to drastic changes in the blood flow<sup>57</sup>. An agent-based model was also used to investigate the influence of red blood cells on blood-mediated nanoparticle<sup>62</sup>. It was shown that polydispersity of nanoparticles is an important factor, which can influence clearance, tissue penetration, and the immune system interaction.

Physiologically based pharmacokinetic models are particularly well suited to predicting nanoparticle transport through the body, where each relevant region is reduced into compartments and where each compartment contains permeability-limited, or perfusion-limited, models that describe how drugs, molecules, or indeed nanoparticles, pass through the individual compartments. The models are parameterised by properties that can be measured *in vitro* or *in vivo*, such as tissue volume or tissue flow rate, while drug-specific properties, such as clearance and tissue partition coefficients, are either scaled based on *in vitro* measurements or found using other *in silico* models where *in vitro* measurements are challenging to obtain. These pharmacokinetic models have been applied to nanoparticle-based drug delivery therapies, predicting, for example, the plasma and tissue concentrations of nanoparticles in mice<sup>63</sup>. For a review of pharmacokinetic models, see, for example, work by Yuan et al.<sup>64</sup>.

Along with transport through the body, it is important to be able to characterise the cytotoxicity of nanoparticle-based treatments<sup>40,63,65</sup>. This is because nanoparticles are often used to address high levels of toxicity caused by other anti-cancer treatments such as chemotherapies, can be given in conjunction with such treatments, and are often administered to

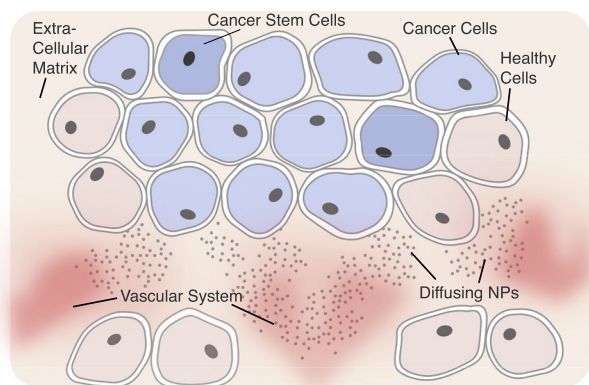
immunocompromised patients. Computational models have been developed to explore the cytotoxicity of these therapies. For example, pharmacokinetic models have been used to investigate the difference in interspecies cytotoxicity, an important factor in translational research<sup>63</sup>. Alternatively, a continuum model of tumour growth was combined with experimental work to evaluate the cytotoxicity of gold nanoparticles carrying chemotherapy molecules<sup>40</sup>. It was shown that nanoparticle-based therapies had an overall increase in efficacy and reduced cytotoxicity when compared to the free drug. For a review of the application of computer models to the cytotoxicity of nanoparticles, see, for example, work by Ding et al.<sup>65</sup>.

One of the many benefits of nanoparticle-based drug delivery is that nanoparticles can be designed to take advantage of the so-called enhanced permeability and retention (EPR) effect which allows the nanoparticles to passively target the tumour. EPR is a result of the leaky angiogenic micro-vessels that cause an increase in the fluid pressure within the tumour<sup>66</sup>. Nanoparticles tend to escape from the enlarged pores in the faulty tumour vascular network into the surrounding tissues. *In silico* investigations have highlighted potential best nanoparticle-design to take advantage of irregularities at the endothelial wall. For example, the influence of increasing vascular permeability has been considered and shown to be beneficial for nanoparticle delivery<sup>36</sup>. However, the EPR effect has substantial variability both temporally and spatially and cannot be assumed for all tumours (it is not found in gastric and pancreatic cancer, for example work by Nakamura et al.<sup>67</sup>). Furthermore, the high interstitial pressure developed in certain tumours can also limit the in-flow of nanoparticles from outside the tumour<sup>68</sup> which can discount the therapeutic usefulness of the EPR effect in humans. Hence, care should be given when assuming this means of passive targeting<sup>68</sup>.

One potential cause for this discrepancy in the usefulness of the EPR effect may lay with the animal models that are used to study it. For example, the rapid angiogenesis that is induced for *in vivo* experiments leads to tumours that grow on much faster timescales than commonly occurring in humans. Furthermore, the ratio of grown animal tumour to the total weight of the animal used will be far higher than that observed in humans. Both these features will promote the extravasation potential of nanoparticles, potentially to unrealistic levels when compared against clinical studies<sup>38,69</sup>. As discussed above, the EPR effect can be strong in some tumours but negligible in others and should not be assumed as a general feature for all tumour types<sup>68</sup>.

The design of the nanoparticles can have implications both for the success of the individual nanoparticles as well as subsequent injections. For example, if large particles are injected first then their reduced diffusive ability can clog extravasation points for successful transport of smaller nanoparticles. This indicates a





**Fig. 3 Considerations when modelling NP transport through the tumour tissue, as well as interactions with cells of different types or other NPs.** NPs (shown as black dots) are shown leaving the vascular system and diffusing through towards endothelial cells. NPs are required to penetrate deep enough through the tumour tissue in order to be effective while aiming to be internalised by specific cell types (cancer cells and cancer stem cells) while avoiding other cell types (such as healthy cells).

possible two-phase extravasation profile where fast extravasation is followed by slow extravasation, highlighting additional design considerations when engineering nanoparticles<sup>69</sup>. The structure of the vascular network will also be influential, especially around the tumour site. For example, spatial irregularities within the network can lead to uneven distribution of drugs. This has been considered in work by Sefidgar et al.<sup>32</sup> where the concentration of drug within the interstitial flow was investigated using a multi-scale model of a heterogeneous and dynamic vascular network around a tumour. By allowing feedbacks between hemodynamic and metabolic stimuli and the capillary network, a more irregular capillary network was generated with high interstitial fluid pressure (IFP) within the tumour, as typically observed in vivo. It was shown that the elevated IFP within this irregular network led to a heterogeneous distribution of drugs around the tumour region, highlighting that static or regular vascular networks may be an overly restrictive assumption when modelling drug delivery.

As extravasation is central to nanoparticle penetration and accumulation, it is important that general design principles are known to optimally extravasate into the tumour. Again, in silico models are of use in testing various designs. For example, Brownian dynamics were used to investigate the influence of nanoparticle diameter and aspect ratio on extravasation and demonstrated that larger aspect ratio increases extravasation by alignment with the streamlines exiting the pore<sup>34</sup>. Alternatively, models that describe nanoparticle vascular transport also include considerations of extravasation to improve model accuracy<sup>36,70</sup>. Both vascular transport and extravasation at the tumour site can be modelled using agent-based models<sup>33</sup>. This has been used to simulate tumour growth with a realistic vessel network structure (when compared against 3D intravital image). Though this has yet to be coupled with a nanoparticle design framework, this may offer a further tool for bioengineers to trial designs prior to in vitro and/or vivo testing.

### TISSUE PENETRATION (TP)

For nanoparticle-based therapies, a substantial challenge is predicting the depth that the NPs are able to penetrate into the tumour and where they accumulate, as shown in Fig. 3. In healthy tissue, the IFP leads to the necessary pressure gradient to transport nanoparticles away from vessels. However, IFP within tumour environments can lead to additional barriers for drug

delivery as well as driving the growth of the tumour. Experiments in vivo have shown that IFP is uniform across much of the tumour but drops significantly at the edge<sup>71</sup>. This uniform pressure creates a diffusive environment across much of a tumour and a steep outward flow around the edge. The diffusive environment within the tumour means that extravasated particles move slowly and can diffuse back into the capillary system rather than entering deeper into the tumour tissue<sup>35,72</sup>. Near the edge of a tumour, there is a risk that the nanoparticles will not be retained, instead being irreversibly pushed by the steep pressure gradient<sup>37</sup>.

In silico models offer a means of understanding the obstacles to tumour penetration. The influence of the IFP on the blood and lymphatic systems and their influence on drug-delivery has been investigated using a combination of fluid dynamics and agent-based modelling<sup>73</sup>. This work demonstrated how drug distribution increases as the lymphatic response decreases, due to a reduction in the clearance of drug-delivery vectors. It also demonstrated that the dual normalising of both the vasculature and interstitial is required to improve drug efficacy in order to simultaneously reduce the IFP within the tumour as well as minimise the heterogeneity of the drug distribution within the tumour tissue.

The heterogeneous distribution of nanoparticles has recently been considered using in silico models that combines the growth of a tumour with angiogenesis and drug delivery<sup>74</sup>. This work used a three-dimensional model continuum approach to highlight conditions of the tumour for enhanced nanoparticle drug delivery such as high interstitial porosity (to enhance nanoparticle transport). Alternatively, the connection between tumour growth and avascular network generation was modelled using a multi-scale approach that coupled tumour growth with nanoparticle transport<sup>75</sup>. The binding affinity of nanoparticles was shown to play a role in the accumulation within the tumour, where those with high binding affinity concentrate near the vessels and that slow nanoparticles failed to penetrate at lethal levels throughout the tumour tissue<sup>76</sup>.

This coupled model of tumour growth, vasculature system and nanoparticle adhesion has since been used as a tool for optimising nanoparticle design<sup>77</sup>. Here, the model was used to find the optimal nanoparticle diameter for accumulation and penetration. Alternatively, a combination of deterministic and stochastic mathematical methods were used to find the optimum size and binding affinity for nanoparticle penetration into a tumour<sup>76</sup>. Such approaches demonstrate the feasibility of integrating in silico methods with nanoparticle design. Other work has also explored broad biodistribution and tissue distribution of drug-antibody conjugates<sup>78,79</sup>. Here, simulations compared the difference in transport profiles between small molecules and larger macromolecular drugs. Four fundamental classes of drug delivery agents were highlighted (those limited by blood flow, vessel permeability, interstitial diffusion, and local binding and metabolism) each of which have strengths and weaknesses.

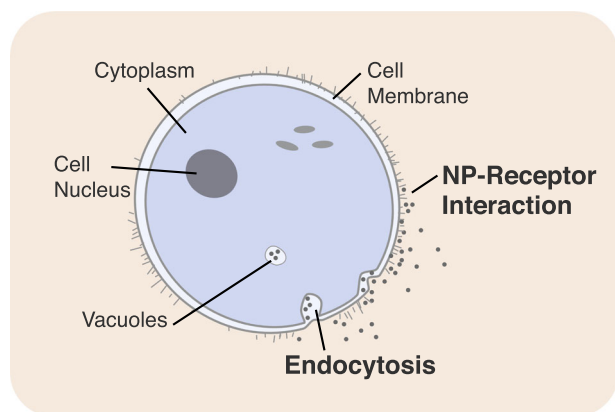
Along with optimising, in silico models have sought to explain why, in some instances, novel drug delivery methods lead to better accumulation and penetration than free-drug alternatives. For example, a general mathematical model was developed to investigate why experimental data showed a 3-fold drop in tumour growth when using nano-vectored drug delivery<sup>43</sup>. This mathematical model combined the cell cycle, vasculature network, and the drug diffusion rates, and was validated using in vivo methods. It demonstrated improved outcome for nanoparticle-based therapies, thought to be driven by the geometry of the particles. In vitro models have also confirmed improved tissue penetration and retention of nanoparticle-based therapies<sup>17,80</sup>. These improvements are thought to be in part due to tumour-scale phenomena such as the vascular network, which prevents certain cells from being reached. Hence, the combination of therapy with vasculature normalisation may provide a further improvement in treatment efficacy.

## ENDOCYTOSIS (END) AND INTRACELLULAR TRANSPORT (IT)

Endocytosis can be performed by various cellular uptake mechanisms<sup>46,81,82</sup>. The rate and mechanism of cellular uptake depends on nanoparticle geometry, coating, and other physico-chemical properties. Yet the specific design of a nanoparticle can greatly improve efficacy. Nanoparticles can be designed to increase cellular uptake (endocytosis) as well as to improve specificity by preferentially targeting cancer cells (through targeting receptors which are found to be upregulated in various tumour cells). Most in silico approaches consider a single nanoparticle or several (no more than ten) nanoparticles on the cell membrane and use either atomistic simulations or coarse-grain approaches such as DPD.

These studies have shown that the size and shape<sup>83</sup>, ligand multi-valency<sup>47</sup> and the role of the protein corona around nanoparticles<sup>45</sup> can all have considerable influence on cellular uptake. For example, super-selectivity was found to occur in multivalent nanoparticles, as they demonstrate 'on-off' binding profiles that is particularly well suited for receptor-concentration selective targeting<sup>47</sup>. This super-selectivity occurs when the fraction of bound particles sharply increases with receptor concentration. In this work, an analytical model was developed and compared against Monte Carlo simulations of nanoparticles with various coatings and general design principles were derived, once again demonstrating the use of in silico models in nanoparticle design. Other work has considered a thermodynamic model for nanoparticle–cell interactions<sup>84</sup> where uptake rates were shown to be strongly related to the size of the nanoparticle and the interaction of multiple nanoparticles with the cell membrane<sup>85</sup>. Both works used coarse-grain approaches. For a comprehensive review of nanoparticle endocytosis see work by Angioletti-Uberti, and Zhang et al.<sup>46,49</sup>.

Having successfully been taken up by the cell, nanoparticles then face the challenge of intracellular transport (see Fig. 4). Post-endocytosis, nanoparticles can be localised at four major intracellular organelles: the cytoplasm, mitochondria, nucleus and lysosome<sup>39</sup>. Nanoparticles inside a cell face the risk of degradation by lysosomes. There are several means of overcoming this risk such as taking advantage of low intra-endosomal pH-induced osmotic swelling and endosome rupture (the proton sponge effect)<sup>38,86</sup>, or by hydrophilic to hydrophobic transition and endosomal membrane destabilisation induced by pH-sensitive amphiphilic polymeric nanoparticles<sup>17,38,87</sup>. Alternatively, a nanoparticle may be required to travel through the cytoplasm for highest effectiveness. However, the diffusion of nanoparticles within the cytoplasm can be significantly reduced due to binding with intracellular objects or the geometry of the nanoparticle.



**Fig. 4 Considerations when modelling NP transport into, and throughout the cell.** NPs (shown as black dots) are internalised through a number of different mechanisms. Here, we show endocytosis and the resulting cell vacuole containing NPs.

Currently, there are no in silico models that deal with intracellular transport at this level of detail.

Molecular dynamics (MD) simulations allow for in silico modelling of cellular uptake and intracellular trafficking of nanoparticles. Such models often give additional data where it is otherwise difficult to monitor the interaction of nanoparticles into and through a cell<sup>36</sup>. For example, MD simulations were used to show that hydrophobic nanoparticles had preferential entry to the endosomal pathway via the caveolae<sup>88</sup>. However, it is expected that additional data is required before models can be improved. Such data would allow for nanoparticles that are engineered with specific physicochemical properties that optimise intracellular transport and localisation in the areas where they finally induce their therapeutic effect. Studies considering nanoparticle geometry and surface functionality have been performed<sup>89</sup>. However, there is some way to go before more general causative effects can be pinpointed. This is further frustrated by the dynamic property of interactions between nanoparticles and intracellular objects and the fact that nanoparticles are often small enough to interact with one or many intracellular regions, simultaneously.

## CURRENTLY AVAILABLE TOOLS

We have discussed the biological barriers that prevent nanoparticle-based drug delivery from effectively treating tumours. In silico models allow for a more efficient means of exploring the nanoparticle parameter space than is possible with in vivo and in vitro models. However, the combination of nanoparticle behaviour within relevant biological models depends on the collaboration of multiple fields of research, including mathematical modellers, experimentalists, and clinicians. As such, free open-source software can streamline the design process by reducing model development time and allow more time for discussions on the most important model features that need to be included.

In Table 1, we give a summary of the tools, highlighting which transport barrier they can be used to address, model features such as the dimensionality, type of modelling framework, the scale and whether nanoparticles or proliferation have to be included, and if the codebase is open-source. We discuss some of these simulation tools in more detail below.

Ultimately, the choice of simulation software will depend on the tumour scenario that is being investigated, as several platforms are specifically designed to describe and address physiological scenarios. One example of this is the recent extension to the popular CHASTE system. CHASTE (cancer, heart, and soft-tissue environment) was designed with the specific goal of being a multi-purpose library for computational simulations of biological problems. The cancer codebase takes the cell-cycle of an individual cell as its lowest unit, allowing the user to alter parameters such as rates of cell division or the oxygen uptake. The cell-cycle model is connected to a tissue cell model which gives the user control of cell functionality including age, type, generation, mutational status and mitosis/apoptosis. The CHASTE library was introduced with functionality for producing both 2D crypts of tumour cells as well as 3D spheroid tumours<sup>90</sup>. More recently, the ability to model vascular transport has led to the publication of a library extension known as Microvessel CHASTE<sup>33</sup>.

Microvessel CHASTE allows for integration of 3D datasets of vascularised tissue to be incorporated into the simulations for comparison between in vitro/vivo and computational simulations. Microvessel CHASTE is able to model microvascular related phenomena including angiogenesis, tumour growth, and osteogenesis. Other computational fluid dynamics packages also capture behaviour within the vascular network but, as they are not designed specifically for biologically realistic environments, they fall out of the scope for this review. For further information

**Table 1.** Potential software tools for modelling nanoparticle transport barriers.

	Transport Barriers	Dimension	Nanoparticles	Open-Source	Scale	Modelling Framework
PhysiCell	TP	2D/3D	No	Yes	Intracellular (with MMBIOS) to tissue	Discrete
TumourSimulator	TP, EV, CC	3D	No	Yes	Tissue to cell	Discrete
VCell	TP	2D/3D	No	Yes	Cell to intracellular	Multiple
Smoldyn	IT, END	3D	Yes	No	Intracellular	Discrete
STEPS	IT, END, TP	3D	No	Yes	Tissue to intracellular	Stochastic events via Giuseppe Algorithm
Chaste	CC, TP	2D/3D	No	Yes	Tissue to cell	Multiple
SSC/NanoDocs	TP, END	2D/3D	Yes	Yes	Tissue to cell	Stochastic events via Giuseppe Algorithm
Tumopp	TP	3D	No	Yes	Tissue to cell	Discrete
CompuCell 3D	TP, EV, CC	2D/3D	No	Yes	Tissue to cell	Discrete
IBCell	TP, CC	2D/3D	No	No	Cell	Discrete

on fluid dynamics as applied to oncology, see for example work by Koumoutsakos et al.<sup>66</sup>.

CHASTE and the subsequent Microvessel CHASTE are examples of combining clinical 3D datasets with computational simulations. There is an increasing number of libraries that offer extensive multi-scale functionality at the point of use, including CompuCell3D, Virtual Cell (or VCell), and PhysiCell. CompuCell3D is capable of modelling cell-scale to tissue-scale behaviour. It has been used to describe morphogenesis as well as cell-cell interactions, the immune response to cancer and spatial models of drug delivery routes for cancer treatment<sup>91,92</sup>. Similarly, VCell covers a wider range of modelling approaches which include continuum approaches (ODEs and PDEs), discrete models, and network models (for modelling intracellular signal pathways). It offers active integration with SpringSaLaD<sup>93</sup>, a simulation platform for modelling mesoscopic systems, but it is not currently open-source. PhysiCell<sup>94</sup> is another multi-cellular library that implements hybrid methods to model 2D and 3D biological systems. It uses agent-based methods at the individual cell level and combines this with BioFVM<sup>95</sup>, a finite volume method specifically designed for biological systems. PhysiCell has been used to model tumours including growth and metastasis<sup>95,96</sup> and extended to consider the signalling pathways through combination of the PhysiCell library with MaBoSS (used to run stochastic simulations of the signalling pathway), to create PhysiBoSS<sup>97</sup>.

Many questions on the effectiveness of nanoparticle-based therapies will depend on the model of interaction between nanoparticles and individual cells. To answer these questions, computational simulations are required that consider individual nanoparticle and their interactions, which ultimately change their dynamics. A computational framework has previously been suggested that specifically considers nanoparticle-scale interactions using both deterministic and stochastic methods<sup>76</sup>. These models used the stochastic simulation compiler (SSC) and led to the NanoDoc platform, a means of crowd-sourcing novel nanoparticle designs through online engagement (<http://nanodoc.org>). One of the most popular purpose-built libraries for modelling intracellular signal pathways is Smoldyn<sup>98</sup>, an agent-based model that can effectively describe nanosecond to microsecond molecular-resolution behaviour. This package is open-source and has been used to describe macromolecular crowding and molecular diffusion. Similarly, the stochastic engine for pathway simulation (STEPS) is an open source package for stochastic simulations of reaction-diffusion systems where the geometry of the domain is important<sup>99</sup>. Originally built to simulate neuronal signalling pathways, the length-scales consider by this package make it a viable tool for nanoparticle research.

Furthermore, STEPS has been shown to effectively compute large-scale simulations using multi-core parallelisation, increasing the size of simulated systems<sup>100</sup>. To the best of the authors' knowledge, neither Smoldyn nor STEPS have yet to be applied specifically to nanoparticle simulation. Finally, there are several molecular dynamic simulation tools that are available which have been used to consider nanoparticle design. While not specific to nanomedicine or oncology, these have been reviewed in, for example, work by Cummings et al.<sup>101</sup>.

## MACHINE LEARNING AND DATA-DRIVEN APPROACHES

All the above discussions have centred on the overlap between in silico models of nanoparticle transport barriers. The current state of the field within nanomedicine is similar to that seen in material sciences, biology, and medicine where multi-scale simulations have led to a far wider exploration of system dynamics than possible prior to increases in computational power and data. However, in recent years the application of machine learning and data-driven methods has led to a significant shift in research methodology and contributed to advances in these (as well as many other) fields<sup>18,102,103</sup>. Moreover, it is expected that the application of these methodologies will accelerate in the future. Hence, it is important to characterise these techniques in relation to nanomedicine.

Describing the current state-of-the-art in machine learning is beyond the scope of this review and has been well described in other work<sup>104,105</sup>. Furthermore, while the application of machine learning tools to the field of nanomedicine is still relatively uncommon, these methods have already been applied specifically to characterisation of drug-loaded NPs. For example, artificial neural networks have been used to predict drug-loaded NP size and polydispersity<sup>106,107</sup>, both having clear implications for the efficacy of nanoparticle-based treatments. Other work has used machine learning tools to optimise cellular uptake, minimise cytotoxicity and predict the development of the protein corona around a nanoparticle<sup>108–111</sup>. For a recent review of this area, see for example, work by Jones et al. and Sason et al.<sup>112,113</sup>. Ultimately, these techniques further benefit from their integration with in silico models, as this leads to a speed up in time and reduction in costs, as output from in silico models become input for machine learning techniques. This has already been seen in material sciences, where algorithmic learning of specific models can massively speed up the exploration of a system's state space<sup>102</sup>.

Whereas the characterisation and design of nanoparticles is expected to greatly benefit from utilisation of machine learning methods, additional benefits can also be gained from the



combination of machine learning with experiment design. Active learning uses machine learning techniques (such as reinforcement learning<sup>114</sup> or surrogate-assisted optimisation<sup>115</sup>) to guide experiment design by selecting for only the most promising candidates that require testing. This approach, distinct from traditional trial-and-error, has already shown promise within the fields of clinical cancer trials, drug discovery and material discovery<sup>18,116,117</sup>. We believe that designing nanoparticles to overcome transport barriers is a rich future area of study<sup>118</sup>. Furthermore, the integration of *in silico* models with active learning will allow for both the automatic exploration and nanoparticle designs, and a way to test them, often a pre-requisite when implementing an active learning approach<sup>102</sup>.

With recent advances in multi-scale simulations of tumours and nanomedicines and their combination with machine learning techniques, the application of *in silico* methods in a clinical setting is beginning to become reality. However, establishing the clinical relevance of computational models requires industry-grade evidence gained through verification and validation, sensitivity analysis, and uncertainty quantification, amongst other things<sup>119</sup>. The level of rigour of these evidences will depend on both their intended use and the clarity of such use at the outset. Hence, the existence of guidance documents is critical in the successful and safe application of such methods to the clinical setting<sup>120</sup>. In 2013, the International Medical Device Regulators Forum (IMDRF) published the first in a series of guidance documents on 'Software as a Medical Device' (SaMD). They covered key definitions<sup>121</sup>, categorisation<sup>122</sup>, quality management system<sup>123</sup> and planning the process for clinical evaluation of a SaMD<sup>124</sup>.

Taken together those documents provide a risk-based framework where the level of clinical evidence depends on the risk profile of a SaMD, where the risk profile is characterised by the severity of the underlying health condition and the significance of the information provided by the SaMD to the healthcare decision maker. Since computational models of physiological systems are usually nonlinear, highly complex, and contain high numbers of parameters and time-dependent properties, their proper assessment can be very challenging. On top of this, the introduction of machine learning into simulation models opens up a new set of problems including lack of transparency, automation bias (where there is a tendency of users to non-critically accept computer recommendations) and changes in input/output relations as an algorithm learns from real-world use and experience. In 2019, the FDA published a discussion paper which calls for medical machine learning algorithms to include the types of anticipated modifications<sup>125</sup>. In light of this, we advise developers, as early as possible in the development pipeline, to get familiar with the possible risks associated with their simulation platform and take into account relevant sources of evidence (such as verification, validation, and uncertainty quantification) that are likely to be required in clinical settings.

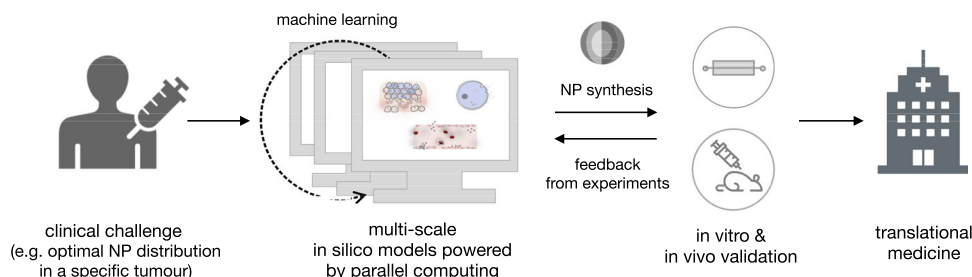
## CONCLUSIONS AND FUTURE PERSPECTIVE

Overcoming nanoparticle transport barriers, specifically travel through the vasculature, extravasation, tissue penetration, endocytosis and the delivery of a therapeutic cargo, is paramount to the effective use of nanoparticles or anti-cancer treatments. *In silico* tools allow for the fast and systematic exploration of the nanoparticle design space to select nanoparticles with the potential to deliver their cargo to the right place. General guidelines extracted from such tools could prove useful in making more effective treatments. Specific solutions could also be provided to tailor nanoparticles to patient needs and towards personalised medicine, or to produce sufficient amounts of data for machine learning. Building useful *in silico* tools will require close validation with *in vitro* and *in vivo* results. The overarching aim is to create a systems approach to nanomedicine which accounts for multi-scale phenomena, which is repeatedly validated, and which exists within a shared modelling framework. We describe these elements in more detail below.

To become effective, nanoparticle cancer therapies require a systematic approach to prototyping. *In silico* modelling has now advanced to the point of being an effective tool that can minimise costly trial-and-error design methods (see, for example, the review by Karolak et al.<sup>59</sup>). However, such modelling cannot exist in isolation and a collaboration between mathematical modellers, experimentalists, and clinicians will be required to inform the best transfer of knowledge. As a first step, this method will help identify guidelines for the design of suitable nanoparticles for a class of problems, say a specific tumour type. In the future, integration of patient data such as MRI scans or biopsies can inform computational models of tumour growth and offer a route to personalised nanoparticles<sup>126,127</sup>. We envisage a pipeline where theoretical predictions are checked against clinical outcomes and then returned to inform future simulations, as shown in Fig. 5.

Tumour progression and nanoparticle transport exhibit clear multi-scale behaviour. This can be understood within a systems biology framework<sup>128,129</sup>; individual microscopic effects are more than the sum of their parts when viewed in aggregate. It is not straightforward to determine the probability distribution of emergent behaviour using microstate characterisation, as the variables in complex biological systems are interdependent and unlikely to be normally distributed<sup>27</sup>. Yet, by testing multiple *in silico* models, a sufficient sampling of the model outputs allows us to project microstate knowledge higher up the hierarchy of scales. This is possible using *in silico* models as system parameters can be closely controlled for and many thousands of possible model scenarios can be investigated in a systematic and efficient way. Using a systems approach to cancer modelling, covering topics such as tissue complexity, cell heterogeneity, targeted therapy, and drug resistance, has been reviewed in, for example, work by Werner et al.<sup>130</sup>.

This system approach highlights three immediate advantages of using multi-scale *in silico* models: improved hypothesis testing, strategy generation, and clinical relevance. Brute force simulation



**Fig. 5 Integrated pipeline for optimised anti-cancer nanoparticle design.** A clinical challenge is identified, *in silico* models are used to design NPs for overcoming this challenge, and iterative synthesis and testing of NPs leads to the development of effective translation medicine.



experiments allow for much wider characterisation and sampling of a systems state-space<sup>73</sup>. These allows the simulations to test whether microstate phenomena have a verifiable causal relation to emergent macroscale observables. This is the hypothesis testing benefit. For example, PhysiCell has been used to run large-scale parallelised simulations that generate data-driven error metrics and create in silico validations of biomedical hypotheses<sup>131</sup>.

Second, the increased sample rate gained from running many thousands of simultaneous simulations generates much larger data. Increased data, combined with optimisation and machine learning, will lead to novel, more efficient, strategy generation<sup>76</sup>. Furthermore, by combining computer simulations with patient data and experimental results, these novel strategies can be implemented and checked to explore new medical applications.

This motivates the third advantage of silico models. In silico models validated and optimised by in vivo and/or in vitro models have both better explanatory and predictive power. The strength of multi-scale in silico models is the ability to bridge length-scales which have traditionally isolated causal factors. By integrating across scales, the predictive power of in silico modelling approaches can be increased with a corresponding expected payoff to clinical relevance. Furthermore, the combination of simulating across scales with parameters gained from in vitro and/or in vivo can expand causal relations beyond scale of observations (such as relating intercellular growth models to the observed change in the size of a tumour). Finally, the combination of these methods with machine learning techniques can be used to build causal models from correlations inferred from big data<sup>103</sup>.

The three advantages of in silico models (improved hypothesis testing, strategy generation, and clinical relevance) will require standardisation between computational models such that relevant benchmarks can be used to compare various in silico approaches. Furthermore, a common design framework which includes shared datatypes will allow for expedited comparison between models that have a shared common input. This has been advocated before<sup>132–134</sup>, but only time will tell whether such a standardisation becomes successful.

## DATA AVAILABILITY

All relevant data are available from the authors.

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## AUTHOR CONTRIBUTIONS

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## COMPETING INTERESTS

The authors declare no competing interests.

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